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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,683	01/09/2007	Donald F. Doyle	820701-1315	9375

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EXAMINER	
JOIKE, MICHELE K	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,683	DOYLE ET AL.	
	Examiner	Art Unit	
	Michele K. Joike	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-47, 61-65, and 67-71* is/are pending in the application.

4a) Of the above claim(s) *32-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-65, 67-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 April 2010* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 32-47, 61-65, and 67-71 are pending, and claims 61-65, and 67-71 are examined. Any rejection of record in the previous Office Action, mailed December 24, 2009 that is not addressed in this action has been withdrawn.

Because this Office Action only maintains rejections set forth in the previous Office Action and/or sets forth new rejections that are necessitated by amendment, this Office Action is made FINAL.

Claim Objections

Claims 67-71 are objected to because of the following informalities: The claims are numbered incorrectly. Claim number 66 is missing. Therefore, the claims should be re-numbered 66-70. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 64 and 65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant claims ligand binding domains (LBDs) and coactivator domains derived from LBDs of receptors and coactivator domains of coactivators, respectively. Variants of the LBDs and coactivator domains are also claimed. The claims read on a broad genus of LBDs and coactivator domains.

The written description requirement for a genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicants were in possession of the claimed invention. In the instant case, the specification does not sufficiently describe a representative number of derivatives or variants of LBDs or coactivator domains by actual reduction to practice or by disclosure of relevant identifying characteristics.

Applicant claims derivatives or variants of LBDs or coactivator domains by function only, without any disclosed or known correlation between the elements and their function. The specification only provides teachings of LBDs or coactivator domains, but not derivatives or variants of LBDs or coactivator domains. The specification does not teach how to make derivatives or variants of LBDs or coactivator domains and still retain the necessary properties to function in the cell as desired. The skilled artisan cannot envision a sufficient number of embodiments of the instant invention from the instant specification because the specification only discloses LBDs or

coactivator domains and only mentions derivatives and variants, and does not disclose any functional derivatives or variants.

The state of the art at the time of filing does not provide sufficient information on the subject to overcome the deficiencies of the instant specification. There is no description in the art that allows one to envision a representative number of derivatives or variants of LBDs or coactivator domains disclosing structural or functional features of derivatives or variants of LBDs or coactivator domains so that one of skill in the art could envision the claimed invention. Thus the skilled artisan cannot consult the art at the time of filing to envision a sufficient number of embodiments of the instant invention to see that the applicant was in possession of the claimed genus.

Neither the specification of the instant application or the state of the art at the time of filing teaches a structure-function relationship for a representative number of derivatives or variants of LBDs or coactivator domains. As a result, the skilled artisan would not be able to envision the claimed invention. Therefore applicant has not satisfied the written description requirement to show the skilled artisan that they were in possession of the claimed genus.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 61, 62, 64, 67 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2008/0263687 in view of US 2005/0158776.

US 2008/0263687 (especially paragraphs 92,132-134, 140, 144, 160, 185, 186, 195, 241) teaches a method of modulating the expression of a gene in a host cell comprising the steps of: a) introducing into the host cell a gene expression modulation system, which comprises a receptor LBD and a DBD; b) introducing into the host cell a gene expression cassette comprising i) a GAL4 response element comprising a domain recognized by the GAL4 DNA binding domain from the first hybrid polypeptide; ii) a promoter that is activated by the transactivation domain of a second hybrid polypeptide; and iii) a gene whose expression is to be modulated; and c) introducing into the host cell a ligand; whereby upon introduction of the ligand into the host, expression of the gene of b)iii) is modulated. The transactivation domain and DNA binding domain can be separated by placing them on two different proteins. The receptor complex typically includes proteins which are members of the nuclear receptor superfamily wherein all

members are generally characterized by the presence of a DNA binding domain ("DBD"), and a ligand binding domain ("LBD") separated from the DBD by a hinge region. The receptor can be human RXR. Preferably, the DBD is a GAL4 DBD, the AD is GAL4 AD, and the response element is an RE from GAL4. Preferably, the host cell is a yeast cell. The cell can also include a separate coactivator, such as ACTR or SRC1, which can bind to the receptor in the presence of the ligand to activate expression of the genetic locus. The genetic locus can be a marker that allows for selection on selective media. However, it does not teach that the ligand is generated by enzymic activity.

US 2005/0158776 (especially paragraphs 2-17) teaches a nucleic acid sequence which encodes a retinol dehydrogenase. Retinol dehydrogenase catalyzes the primary and rate-limiting step in the synthesis of retinoic acid from retinol. Retinoic acid receptors (RARs; -alpha, -beta, and -gamma) are retinoid-activated transcription factors, which mediate effects of retinoids on gene expression. Binding of retinoic acid activates the receptors that interact with signaling pathways. Retinol dehydrogenase can be mutated.

The ordinary skilled artisan, desiring to use a ligand that is generated by an enzyme would have been motivated to combine the teachings of US 2008/0263687 teaching a yeast cell with a gene expression modulation system, coactivator and nucleic acid construct comprising a response element linked to a genetic locus, wherein a ligand binds the RXR receptor in the gene modulation system, as described above, with the teachings of US 2005/0158776, teaching that the ligand, retinoic acid (which binds to RXR) can be generated by retinol dehydrogenase, because US 2005/0158776 states

that retinoic acid is a powerful regulator of gene expression; novel retinol dehydrogenases are useful for modulating the synthesis of retinoic acid and, therefore, are useful for modulating gene expression in numerous important biological systems. It would have been obvious to one of ordinary skill in the art to use an enzyme to generate retinoic acid because retinol dehydrogenases generate retinoic acid, and the retinol signaling pathway plays an important role in human disorders and diseases. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 63 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2008/0263687 and US 2005/0158776 as applied to claims 61, 62, 64, 67 and 71 above, and further in view of Chen et al.

US 2008/0263687 and US 2005/0158776 teach all of the limitations as described above. However, they do not teach a coactivator domain operably linked to a transcriptional activator.

Chen et al (Cell 90: 569-580, 1997, especially p. 570) teach ACTR (coactivator of RXR) operably linked to a yeast GAL4 activation domain.

The ordinary skilled artisan, desiring to use a coactivator operably linked to a yeast GAL4 activation domain would have been motivated to combine the teachings of US 2008/0263687 teaching a yeast cell with a gene expression modulation system,

coactivator and nucleic acid construct comprising a response element linked to a genetic locus, wherein a ligand binds the RXR receptor in the gene modulation system, as described above, with the teachings of US 2005/0158776, and with the teachings of Chen et al, because US 2008/0263687 teaches that separating the transactivation and DNA binding domains by placing them on two different proteins results in greatly reduced background activity in the absence of a ligand and significantly increased activity over background in the presence of a ligand. They also teach that the coactivator can be a separate protein and is useful for mediating transcription activation by stimulating DNA binding of transcriptional activators. And Chen et al teach ACTR operably linked to the GAL4 AD. Therefore, it would have been obvious to one of ordinary skill in the art to operably link the coactivator with a transcription activator because coactivators were known to useful for mediating transcription activation by stimulating DNA binding of transcriptional activators, so combining these known elements would lead to the predictable result of activating transcription. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 67-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2008/0263687 and US 2005/0158776 as applied to claims 61, 62, 64 and 71 above, and further in view of White.

US 2008/0263687 and US 2005/0158776 teach all of the limitations as described above. However, they do not teach that the genetic locus inhibits proliferation of the cell on selective medium, that the selective medium comprises 5-FOA, or that the genetic locus encodes orotidine-5'-phosphate decarboxylase.

White (PNAS 93: 10001-10003, 1996, especially p. 10001) teaches the use of marker URA3 (which encodes orotidine-5'-phosphate decarboxylase), which is essential for uracil biosynthesis and can also catalyze the transformation of 5-FOA into a toxic compound. 5-FOA can be present in the media. URA3 can be controlled by a promoter containing GAL4 binding sites.

The ordinary skilled artisan would have been motivated to combine the teachings of US 2008/0263687 teaching a yeast cell with a gene expression modulation system, coactivator and nucleic acid construct comprising a response element linked to a genetic locus, wherein a ligand binds the RXR receptor in the gene modulation system, as described above, with the teachings of US 2005/0158776, with the teachings of White because White teaches that using URA3 and growing the cell on media lacking uracil can be used to require interaction of the DBD and AD, while growing the cell on media containing 5-FOA can be used to inhibit growth by interacting the DBD and AD, in other words, positive and negative selection. It would have been obvious to one of ordinary skill in the art to use URA3, because URA3 is a widely used selectable marker and can be tightly controlled by a regulated promoter containing Gal4 binding sites. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary,

that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Allowable Subject Matter

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele K. Joike whose telephone number is (571)272-5915. The examiner can normally be reached on M-F, 10:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michele K. Joike/
Primary Examiner, Art Unit 1636

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